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Evaluation of Follow-Up Investigations in Osteosarcoma Patients: Suggestions for an Effective Follow-Up Program

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Background and Procedure. Follow-up programs for cancer patients aim at improving the overall prognosis by early detection of relapse. In this study, follow-up data from 72 osteosarcoma patients were received in order to determine the value of clinical examination (CE), lung CT-scan (CTL), chest X-ray (CXR), local X-ray (LXR), and bone scintigraphy (BS) in the detection of tumor recurrence.

Procedure. Twenty-eight of 72 osteosarcoma patients presented with a total of 61 relapse sites. A continuous remission after relapse treatment could be achieved in 2/16 patients with first lung metastases, in 2/6 patients with local relapse, and in 3/19 patients with more than one lung metastasis. More than 90% of all relapses occurred within 3 years off primary therapy, respectively, within 3 years after detection of relapse. Local relapse and lung metastases were primarily diagnosed by CXR, CTL and CE. BS was the most important investigation to detect distant metastases. No relapse was found by routine X-ray of the primary tumor site.

Conclusions. To improve efficacy of follow-up programs and to reduce radiation load of nonrelapsed patients, the prognosis of patients with lung metastases or local recurrences and the time of high risk for a relapse should be taken into consideration. Since the number of patients who benefit from relapse therapy is still low, it remains to be shown whether an increased frequency of lung CT-scans or MRIs of the primary tumor site will improve early detection of relapse; and if so, whether that will enhance the chance for successful relapse treatment.

CXR, CTL and CE should be performed routinely for at least 3 years after completion of therapy or relapse diagnosis. In contrast, BS and LXR appear not to be useful as routine investigations. Med. Pediatr. Oncol. 30:52–58, 1998. © 1998. Wiley-Liss, Inc.

Key words: osteosarcoma; follow-up; relapse; prognosis

INTRODUCTION

Osteogenic sarcoma is the most frequent malignant bone tumor in adolescence. Since in about 80% of patients occult micrometastases exist at the time of diagnosis, prognosis was improved by introduction of polychemotherapy. Treatment regimens using adjuvant or neoadjuvant chemotherapy have led to a relapse-free survival rate of about 60% [1–3]. Intensive follow-up programs might further improve the prognosis in patients with osteosarcoma by detection of relapse at an early enough stage when continuous remission of relapsed tumor can still be achieved.

In the time before the introduction of polychemotherapy, almost all patients with relapse presented with lung metastases as the first relapse site [4, 5]. Thus, extended follow-up investigations were not needed [6]. Improvement of survival with adjuvant or neoadjuvant chemotherapy changed the relapse pattern [7], showing that the initial metastasis could also be local or distant bone relapse before a lung metastasis developed. However, the outcome of patients with various metastases show that those patients with multiple bone metastases or with more than one relapse have a poor prognosis [8–12]. This ought to be taken into consideration for an effective follow-up program.

Vanal et al. [13] compared the sensitivity of standard radiography and scintigraphy with CT scans for the detection of pulmonary metastases in patients with osteogenic sarcoma. They found the sensitivity of standard X-ray to be 57% of that of CT-scans. The sensitivity of scintigraphy was much lower (23%). However, the comparison of CT-scans and CXR shows that CT-scans not only detect more metastases but in some case also nodules which showed no evidence for malignancy on histological examination [14]. Thus, the higher sensitivity of CT-scans might in some cases lead to unnecessary surgery. In addition, radiation load and cost of CT-scans are higher than for standard radiography. Therefore, it needs to be determined whether routinely performed CXR might be a sufficient investigation for the detection of pulmonary metastases at a resectable stage.

Rieden et al. [15] found that in osteosarcoma, bone

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scintigraphy was the most sensitive method for detecting both metastatic bone tumor and relapse at the primary site, probably because these tumors show a typical pattern of tracer uptake [16–21]. In a previous study we could show that about 1.5% of routinely performed bone scintigraphies demonstrated a relapse [22]. However, McKillop et al. [7] showed that in 50% of relapsed patients, scintigraphy could demonstrate the recurrence before it became clinically symptomatic. Thus, bone scintigraphy might be useful for early detection of bone relapse and improvement of prognosis. However, tracer enhancement by bone scintigraphy could also be a result of trauma, infection or body malactivity in patients with limb amputation. Misinterpretation of these findings as a relapse or suspicion of relapse might lead to further unnecessary investigations with high cost and radiation load [22]. Therefore, a critical review of the role of bone scintigraphy for the detection of relapses in osteosarcoma patients might be important.

Clinical examination of patients with osteosarcoma as part of a routine follow-up program might be valuable to detect metastatic disease. In contrast to radiographic studies, clinical evaluation bears no risk for the patient. However, the value of clinical examination for the detection of relapse beyond initial therapy of osteogenic sarcoma has never been evaluated and compared to diagnostic imaging techniques.

In this study, data on 72 patients with osteogenic sarcoma were reviewed in order to determine which patients might benefit from an intensive follow-up program. In addition, the period of an increased risk for a relapse was analyzed. Finally, it was evaluated which follow-up investigations actually helped detect relapse in osteosarcoma patients.

PATIENTS AND METHODS

The clinical records of 72 patients with osteogenic sarcoma were reviewed in this study. Patients had been treated at the Department of Pediatric Hematology and Oncology of the Heinrich-Heine University Medical Center between 1978 and 1992. Patient age ranged from 2 to 21 years (median 14 yr). Patients were treated according to the current T-7 and COSS 77, 82, 85 and 89 protocols [9,10,23–25] including polychemotherapy and tumor resection. Relapse treatment included relapse chemotherapy using VP-16 and Carboplatinum, and/or tumor resection.

During follow-up, patients received a CT-scan of the lung directly after completion of therapy. Local X-ray of the initial tumor sites and 99m Technetium methylene diphosphonate bone scintigraphy were performed every 3–6 months during the first 2 years off therapy. Between the third and fifth year off therapy, both investigations were performed annually. Chest X-rays were taken monthly or bimonthly during the first and second years off therapy. Between the third and fifth year, they were performed every 4 to 6 months and thereafter annually until the tenth year off therapy.

RESULTS

In a retrospective study, patient records of 72 children and adolescents presenting with osteogenic sarcoma were analyzed. Twenty-eight patients suffered a total of 61 relapses. In addition, three patients died of HIV infection, cardiomyopathy or anorexia. Therefore the disease-free survival was 61% and the overall survival was 67% with a median observation period of 5 years. Three patients presented with lung metastases at initial diagnosis; of these, two patients survived without relapse.

After relapse, a continuous remission could be induced in 7/28 patients. Two patients with a first lung metastasis and two patients with a first local relapse survived without further relapse. In addition, three patients with a second, third or fourth pulmonary metastasis survived (Fig. 1). The median follow-up period of these patients was 10 yr (range: 3–13 yr). In contrast, 0/6 patients with first distant metastasis and 0/6 patients with distant metastasis as second, third or fourth relapse survived despite relapse treatment.

A total of 28 first relapses occurred during therapy up until 5 yr after the end of therapy. All local and distant relapses as well as more than 95% of all lung metastases were diagnosed within the first 3 years off therapy (Fig. 2). However, lung metastases were also observed as late as 5 yr after completion of chemotherapy. Eighteen patients suffered a total of 33 second or further relapses. These relapses mostly occurred as lung metastases (18/33), followed by distant relapses (14/33). Thirty-two of 33 relapses were observed within 3 yr after relapse diagnosis.

The time between initial diagnosis and first metastasis correlated significantly with the outcome after relapse therapy. While 4/10 patients in whom the first relapse had developed beyond 12 months off therapy survived without further relapse, 0/18 patients stayed in remission after relapse therapy, when the relapse had developed before 12 months off therapy ($p < 0.05$).

During the follow-up program of patients with osteosarcoma, a total of 60 CT-scans, 541 bone scintigraphies and 1,438 chest X-rays were performed. To determine whether all these investigations were necessary for a successful follow-up program, it was analyzed which follow-up studies led to the detection of relapse.

In patients with lung metastases, the first relapse was most commonly detected by routine CXR (13/16 patients). In three patients, either clinical symptoms such as coughing, bone scintigraphy or CT-scan lead to detection of these relapses (Fig. 3). However, only 2/16 patients

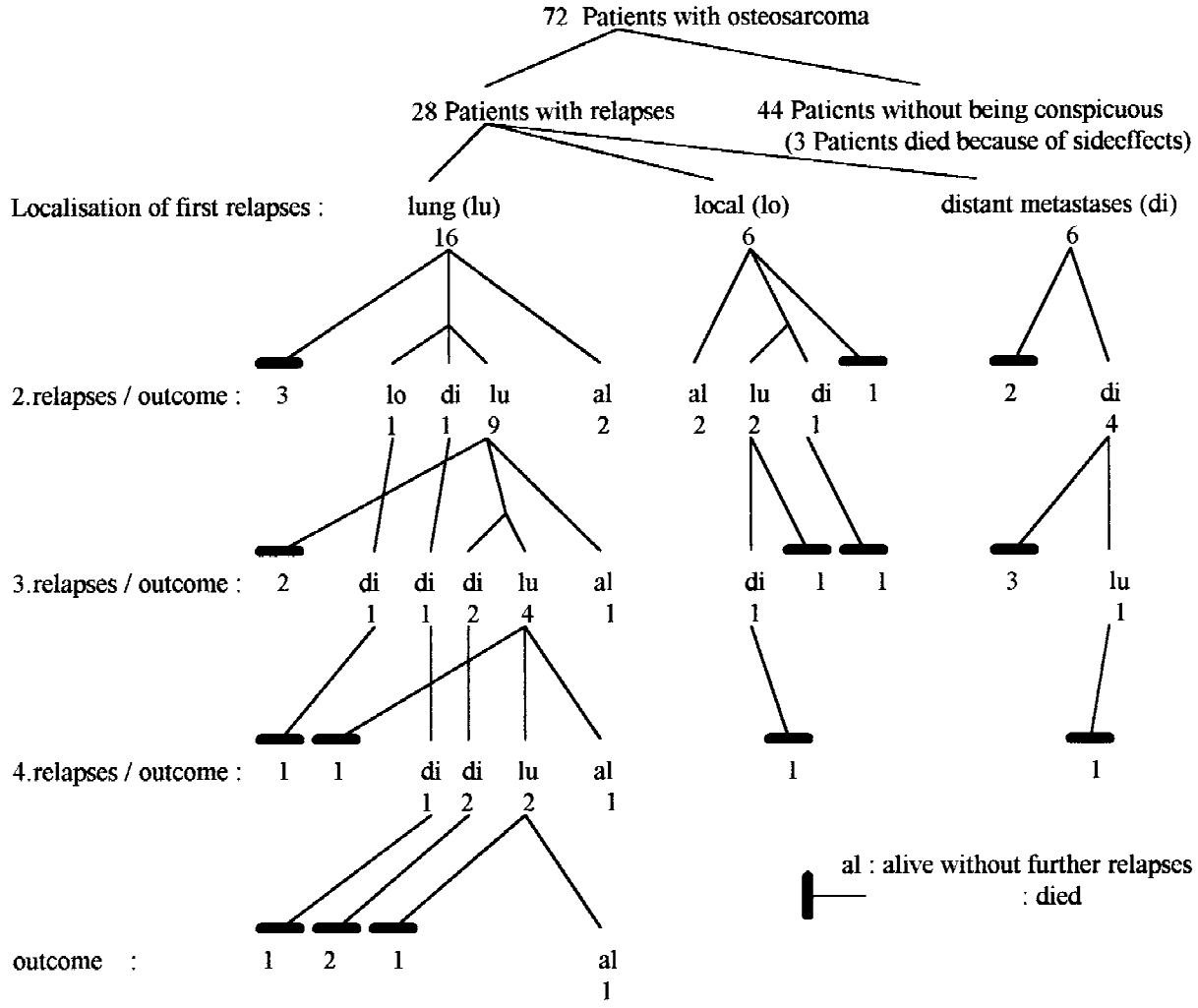

Fig. 1. Clinical course of patients with metastatic osteosarcoma. Clinical data of 72 patients were reviewed. Indicated are relapse sites for the first to fourth relapse. In addition, the clinical course of each of the 28 patients with at least one relapse after treatment for osteosarcoma is indicated by arrows. The results show that seven patients, five with lung metastases and two with local relapse, survived the metastatic disease.

continue to be in remission without further relapse (Fig. 1). In these patients the relapses were detected by CXR.

First distant metastases were identified by bone scintigraphy (3/6 patients [pt]), CT-scan of the lungs (1 pt), CXR (1 pt) and indolent lymphadenopathy detected on routine clinical examination (1 pt, Fig. 3). However, in none of these patients was a second continuous remission achieved (Fig. 1).

In six patients, first local relapse was detected by clinical symptoms such as pain and/or swelling at the primary tumor site (5/6 pt) or by bone scintigraphy (1/6 pt). Primary tumor sites included humerus (1 pt), pelvis (2 pt), proximal (1 pt) or distal femur (1 pt) and proximal tibia (1 pt). Two of 6 patients with a tumor of the distal femur or the proximal tibia continue to be in remission. In one patient, the relapse was detected during routine clinical examination. In the second patient, the relapse was diagnosed by painful swelling of the primary tumor site which led to clinical examination.

In patients with more than one relapse, these relapse sites were detected by CT, CXR, scintigraphy and clinical examination (Table I). However, only three patients with lung metastases survived. In two cases, diagnosis was made by CXR. In one patient with a third relapse of a lung metastasis, detection was only possible by CT-scan due to scarring of the lungs secondary to surgery.

DISCUSSION

After introduction of polychemotherapy, the prognosis of patients presenting with osteosarcoma improved from 20% to about 60% [1–3]. Kaplan-Mayer analysis of the patient group studied here revealed an event-free survival rate of 61% which was comparable to the findings of the COSS studies [9, 10, 23–25]. Thus, in this investigation, a representative group of osteosarcoma patients was followed.

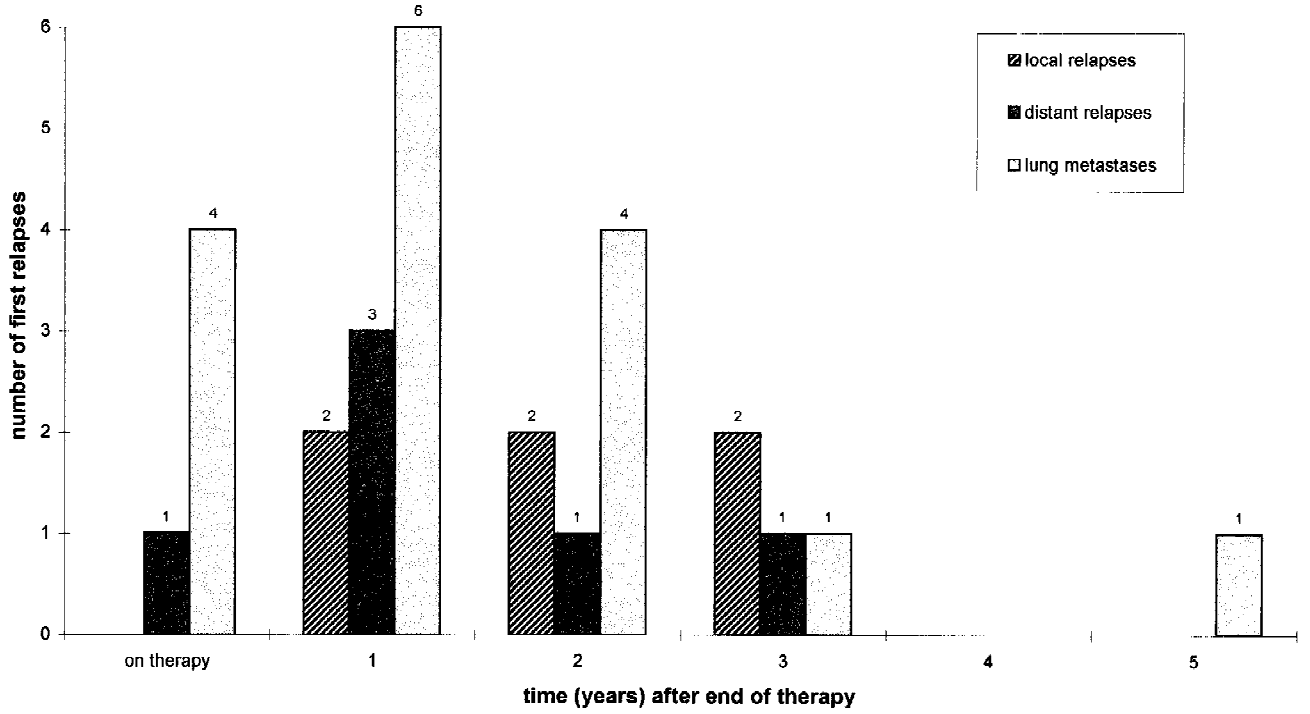

Fig. 2. Correlation between time of first relapse and relapse site. Clinical data of 72 patients were reviewed to determine the number of relapses at a certain location (y-axis) and the time after diagnosis of osteosarcoma (x-axis).

Recently, there has been some debate as to whether intensive follow-up programs for cancer patients can improve prognosis by detecting relapse at stages when successful relapse therapy is still possible. In our study we could demonstrate that about 25% of relapsed patients could be saved by relapse therapy, probably due to early detection of relapse. However, in order to detect these relapses, numerous investigations associated with high radiation load and high cost were made in patients who never relapsed. In this study, we reviewed patient charts from 72 adolescents who had been treated between 1978 and 1993 at our department to determine which patients might benefit from an intensive follow-up program.

A successful relapse therapy was possible in five patients with lung metastases and in two patients with local recurrence of the tumor. These results are in keeping with those of Tabone et al. [26] who analyzed the outcome of 137 pediatric patients with osteosarcoma. They showed that recurrences at the primary tumor site as well as lung metastases had a good prognosis compared to patients with distant or multiple metastases. Thus, with respect to high cost and radiation load, investigations which aim at the detection of multiple sceletal metastases such as total body bone scintigraphy ought probably not to be included in a routine follow-up program, at least as long as no effective high-dose protocols for patients with distant or multiple relapses are available.

The period when most relapses occur might also be considered for the planning of an effective follow-up program. Most first relapses in the patients reported here developed within 2 or 3 years off therapy. The time when the relapse developed was critical for the outcome after relapse therapy and occurrence of the relapse beyond the first year off therapy was correlated with a significantly better prognosis similar to the results reported by others [27, 28]. However, 2/10 patients in whom lung metastases developed under therapy or during the first 12 months off therapy survived after a second or third lung metastasis, indicating that even patients with early metastatic disease might benefit from a relapse therapy provided the metastasis is detected when still curable. Thus, a follow-up program for nonrelapsed patients should be performed at least during the first 3 years after completion of initial treatment. Since second to fourth relapses occurred much earlier after diagnosis of the first relapse site, the time frame for an intensive follow-up program for these patients might be even limited to 2 years off relapse treatment.

First pulmonary metastases were found in about 60% of our patients similar to the results of other studies [29–31]. Survival of patients with pulmonary secondaries is closely correlated with complete resection of the metastases by an experienced surgeon [29–36]. Resectability, however, is dependent on the extension of the metastasis, i.e., number of nodules, size of metastasis and uni- or bilateral localisation. Bilateral extension of pulmonary metastases and more than four nodules were correlated with a poor prognosis [37, 38].

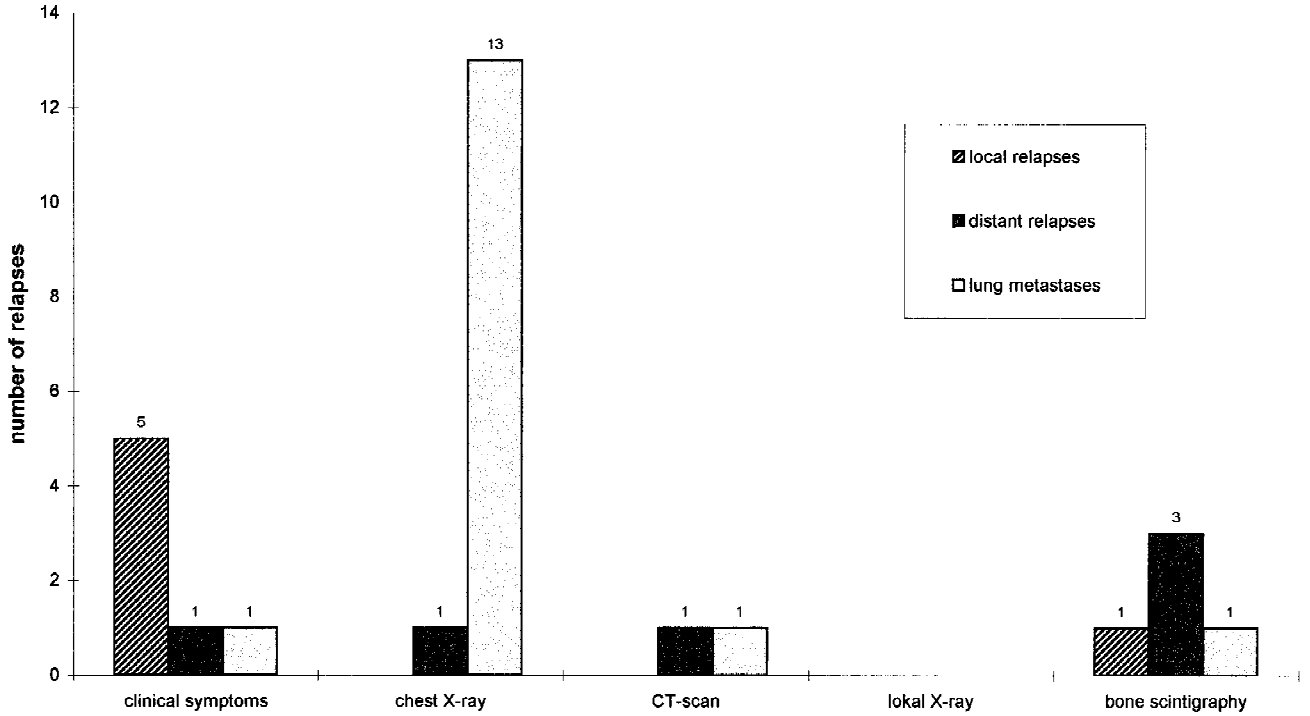

Fig. 3. Detection of first relapse. In 28 patients, first relapse of the osteosarcoma was diagnosed. Relapse was first diagnosed by clinical symptoms, bone scintigraphy, chest X-ray or CT-scanning as indicated on the x-axis.

TABLE I. Relapse Diagnosis in Patients With More Than One Relapse

	Detection by			
Relapse site	CT-scan	X-ray	Scintigraphy	Clinical examination
Lung metastases	4	10	2	2
Distant metastases	0	3	1	10
Local relapse	0	0	0	1

A comparison of CT-scans and CXR showed that nodules were detected earlier by CT scans and that the size of the detected nodules was smaller [13, 39]. Therefore, these investigators suggested to perform CT-scans every 3 to 6 months during the first 2 years after therapy. However, these studies did not analyze if the use of CT-scans could improve the chances for a successful relapse therapy when compared with a follow-up program using CXR alone. In our study, 5/19 patients with pulmonary metastases survived after relapse treatment (median follow-up period: 10 yr) although follow-up investigations included only routine CXR. These results are similar to those obtained by others who used routine CT-scans of the lung for follow-up [34–38]. In these investigations, 5-year survival of patients with pulmonary metastasis was reported as 25.8% (38), 23% (37), 17% (34), 32% (35), and 40% (36), respectively, suggesting that survival of patients was dependent on factors which were independent of the follow-up program.

The number of pulmonary metastases is higher in patients with early relapse [35, 36, 40], and patients with early relapse have a significantly worse prognosis [35, 36, 41]. Thus, the biology of the tumor might determine the outcome of the patients and it is questionable whether better detection of lung metastases by CT-scan compared to CXR could actually help improve the prognosis of these patients. However, CT-scanning carries a higher radiation load and the cost is about fivefold higher than for CXR. Therefore, a prospective and randomized study is needed to answer this question.

In our study, 2/6 patients with local relapse survived after relapse treatment. These numbers are in keeping with those reported by Glasser et al. [42]. Most local relapses were detected by clinical symptoms either during routine follow-up examination or during extra consultation, indicating that these relapses were detected relatively late. This is further emphasized by the observation that 3/6 patients with local relapses died from distant metastases, indicating a spread of tumor cells. Imaging techniques such as local roentgenogram and bone scintigraphy generally failed to improve the detection of local relapse. Therefore, it should be evaluated whether newer techniques such as MRI could help improve the detection of local relapse before they become clinically evident. Since MRI studies are very expensive (about 10 to 15 times more than local X-ray), these studies might not need to be performed in all patients. Since

patients with proximal tumors, en bloc resection of the tumor or marginal resection have a significantly increased risk of local relapse [42, 43], MRI studies might be limited to these patients.

CONCLUSION

This study showed that a routine follow-up program can help detect metastases in osteosarcoma patients at a stage when continuous remission can still be achieved by relapse treatment. However, cost and radiation load of investigations should be minimized without compromising therapeutic benefit. Therefore, the prognosis of relapsed patients, the peak incidence of relapse and the impact on survival probability of imaging techniques for the detection of relapse should be considered. From the results presented here it appears that clinical examination, CXR and lung CT-scan should be performed routinely for at least 3 years after initial or relapse diagnosis. Further studies are needed to determine whether survival would be improved by earlier detection of lung metastases through an increased frequency of lung CT scans. Additional study is also needed to establish whether the use of local MRI scans to detect local relapses before they become clinically evident will improve prognosis.

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